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Review

Catheter ablation of atrial fibrillation: Past, present, and future directions

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice. Because of inadequate efficacy of pharmacological therapy, catheter ablation of AF has evolved dramatically over the last decade. Although the success rate of ablation has improved, the ablation strategy is still extensive, and the ablation procedure is technically challenging. In the past decade, electrophysiologists were eager to obtain high success rates with extensive ablation. In the present decade, further clarification of the complex mechanism of AF is required to make ablation of AF safer and much more efficient. Because the mechanism of AF is very complex, and even somewhat mysterious, it may not be easy to attain a better understanding of the mechanism involved or to discover better guidance for catheter ablation. However, it is important to note that research into AF leads to better understanding of other cardiac and non-cardiac diseases because AF develops multifactorially in association with underlying systemic pathophysiologies.

Contents

1. Introduction . . . 83
2. Patient selection according to the current guidelines . . . 84
3. Patient selection and reverse remodeling after ablation . . . 84
4. History of ablation strategies . . . 84
5. Do we need complete isolation of all PVs in every patient? . . . 84
6. Relation between hemodynamic status and AF . . . 85
7. Advances in technology to isolate PVs . . . 85
8. Ablation of persistent AF . . . 85
   8.1. Efficacy of ablation of complex fractionated atrial electrograms (CFAEs) . . . 85
   8.2. Atrial tachycardia and efficacy of linear ablation . . . 86
   8.3. Ablation endpoint . . . 86
9. The mechanism of persistent AF from the procedural point of view. . . . 86
10. Complications. . . . 87
11. Future direction . . . 88
Conflict of interest . . . 88
References . . . 88

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice. The number of people with AF in the United States is currently estimated at 2.4 million, and the projected number with AF may exceed 10 million by 2050 [1,2]. Treatment for AF is also an important societal issue in that it represents a significant health care cost, currently estimated to be about €13.5 billion annually in the European Union [4]. Increased stroke risk in the presence of AF, reported to be an almost fivefold excess [5], makes AF more than a simple cardiovascular disease.

Because of inadequate efficacy of pharmacological therapy, catheter ablation of AF has evolved dramatically over the last decade. Although the success rate of ablation has improved to $\geq$ 80% with multiple procedures, ablation strategy is still extensive and the ablation procedure is technically challenging,

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resulting in a very high rate, around 50%, of redo procedures. The past decade was an era when electrophysiologists were eager to obtain high success rates with extensive ablation. In the present decade, we are required to further clarify the complex mechanisms of AF to make ablation of AF safer and much more efficient. The ultimate idea is to precisely tailor ablation strategy to the particular AF mechanism of the patient.

2. Patient selection according to the current guidelines

It is important to recognize that the primary justification for an AF ablation procedure at this time is the presence of *symptomatic* AF, with the goal of improving patient quality of life [6]. Although other reasons for performing AF ablation may be justified, such as to decrease stroke risk [7], decrease heart failure risk, and improve survival, they have not yet been systematically evaluated as part of a large randomized clinical trial and are therefore unproven. In the AFFIRM trial, there were no significant differences in the all-cause deaths between rhythm control and rate control using antiarrhythmic drug therapy [8]. However, the beneficial effect on the survival of restoration of sinus rhythm might be offset by the adverse effects of antiarrhythmic drugs. Therefore, sinus rhythm may be preferred over rate control if it can be achieved by catheter ablation. Large prospective multicenter randomized clinical trials will be needed to definitively determine whether sinus rhythm achieved with ablation techniques lowers morbidity and mortality as compared with rate control alone or treatment with antiarrhythmic therapy.

3. Patient selection and reverse remodeling after ablation

Left atrial (LA) size has been established as a prognostic marker of cardiovascular morbidity, mortality, and stroke [9,10]. Studies have shown that LA enlargement and function can improve, i.e., "reverse remodeling," after restoration of sinus rhythm from AF with certain medications or catheter interventions, including radiofrequency ablation [11–13]. A reduction in LA volume may lead to the improvement in LA function and exercise tolerance [14,15], decreased likelihood of thrombus formation [16], and decreased susceptibility to further atrial arrhythmias [13,17]. Although these benefits need to be proven by large randomized prospective trials, reverse remodeling after ablation appears to justify a more aggressive clinical approach even in less symptomatic patients. Currently, 2 studies have reported echocardiographic predictors, including LA strain and strain rate, of LA reverse remodeling after ablation [11,13]. It may be meaningful to select patients who are likely to achieve reverse remodeling as suitable candidates for catheter ablation of AF.

4. History of ablation strategies

After Haïssaguerre et al. reported that the ectopies from pulmonary veins (PVs) are responsible for the initiation of AF, eliminating triggers from the PVs was emphasized as a reasonable approach to treat AF. However, this approach, directly targeting focal triggers, was fraught with high recurrence rates due to the infrequency with which AF initiation could be reproducibly triggered during the catheter ablation procedure, as well as an attendant small risk of PV stenosis.

Segmental ostial ablation was the first catheter-based technique found to electrically isolate the PVs [18,19]. Ablation was performed at the ostia of the PVs, and the acute endpoint of PV isolation (PVI) could be reached in nearly every patient. However, the long-term success rates are relatively modest (60–70%). Circumferential PVI (almost equal to wide-area antral PVI), which involves creating circumferential lesions at the PV antra around the ipsilateral PVs, improved outcomes in patients with both paroxysmal and persistent AF (Fig. 1) [20]. The superiority of circumferential PVI over segmental PVI can be explained by the following: circumferential PVI may extinguish the triggers and drivers located in less common trigger sites other than the PVs, including the antral region of the PVs, the vein and ligament of Marshall, and the posterior LA wall. Circumferential PVI may impact not only triggers but also the arrhythmogenic substrate stabilizing the maintenance of AF [21]. The reduction of atrial muscle mass may make coexistence of multiple reentries impossible (debulking effect) [22]. Moreover, circumferential PVI may interrupt sympathetic and parasympathetic innervation from the autonomic ganglia, which have been identified as potential triggers for AF [23]. In a series of 349 consecutive patients undergoing circumferential PVI at the University of Michigan, AF was eliminated in 87% of patients with paroxysmal AF and 75% of patients with persistent AF [24].

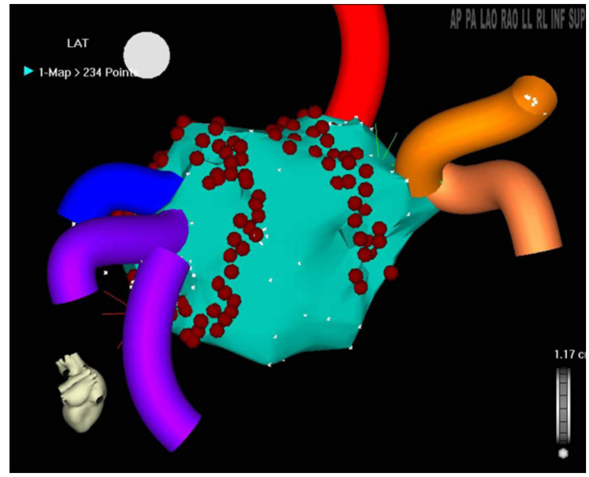

Fig. 1. Circumferential pulmonary vein isolation. The 3-dimensional geometry of the left atrium and pulmonary veins was constructed with the CARTO system.

5. Do we need complete isolation of all PVs in every patient?

Circumferential PVI results in satisfactory outcomes for ablation of paroxysmal AF, and electrical isolation of all PVs is currently a standard approach to the treatment of AF, as recommended by the expert consensus statement [6]. Complete isolation also seems to be important for preventing recurrent atrial tachycardia during follow-up [25–27]. However, it is not clear whether all patients with AF need to undergo isolation of all PVs. A number of studies have reported favorable outcomes with an ablation strategy that does not include PVI. Lemola et al. reported that a successful outcome after LA ablation was found to be independent of the number of PVs that were electrically isolated. Therefore, complete isolation of the PVs was not necessary for a successful outcome [21]. Oral et al. reported that a tailored ablation strategy that targeted driver tachycardias and complex electrograms in the selected PVs resulted in freedom from recurrent AF in ~80% of patients with paroxysmal AF [28]. Pokushalov et al. reported that selective ganglionated plexi ablation directed by an anatomic approach resulted in successful outcomes in ~80% of patients with paroxysmal AF [29]. In the Pratola et al. study [29], patients with persistent AF who underwent PVI and did not have AF recurrence underwent repeated electrophysiological studies. Notably, PVI persisted in only ~40% of the previously isolated PVs. This study supported the idea that atrial substrate also plays an important role in the persistence of AF, and the presence of PV reconnection does not necessarily mean recurrence of AF [30].

In contrast, there is consensus that in the majority of patients, AF recurs in association with recovered PV conduction. In a long follow-up study (median follow-up period of 4.8 years), recovered PV conduction was observed in 62 of 66 patients (94%) at the 2nd ablation procedure [31]. The discrepancy in the impact of PVI on the maintenance of sinus rhythm may be explained by the interaction of a trigger and a substrate. The presence of AF substrate in addition to PV reconnection makes the atria more susceptible to recurrent AF than does PV reconnection alone. However, little data directly supports this notion because the actual prevalence of PV reconnections in patients free from recurrence of AF cannot be evaluated in routine clinical practice.

These studies have indicated that aiming for isolation of all PVs might be an excessive treatment for some patients. However, the critical issue is that during the procedure we never completely know which PV is the trigger that initiates AF (the so-called arrhythmogenic PV) and which PV is not arrhythmogenic. If we could determine this, the efficiency of AF ablation would improve dramatically. Advances in technology to make achievement of isolation of all PVs (so-called prophylactic PVI) safer and easier, especially in paroxysmal AF, may resolve the issue that the arrhythmogenic PV critical to the initiation and perpetuation of AF cannot be definitively determined during the procedure.

6. Relation between hemodynamic status and AF

AF and heart failure create a vicious circle: heart failure promotes AF, and AF aggravates heart failure. In patients with symptomatic heart failure, the prevalence of AF ranges from 10 to 30% [32]. The importance of atrial stretch associated with an increase in atrial pressure in the maintenance of AF has been reported in animal models [33] and in patients with AF [34]. In the human study, patients with persistent AF had significantly higher LA pressures than did patients with paroxysmal AF. The atrial activation rate is known to be higher in patients with persistent AF than in patients with paroxysmal AF. Higher LA pressure may result in a greater degree of stretch-related electrical remodeling and an increase in atrial activation rate, making spontaneous termination of AF less likely.

A potential new risk factor for AF, stiff LA syndrome, was recently proposed. The syndrome itself was originally reported in the late 1980s [35]. Its principal feature is that right heart failure is disproportionate to left heart failure because of reduced LA compliance or LA diastolic dysfunction. Recent studies have indicated that one of the causes of the syndrome was LA ablation for AF [36,37]. Machino-Ohtsuka et al. reported that pre-existing LA stiffness was related to AF recurrence after ablation [38]. Using magnetocardiography analysis, Sato et al. showed that right atrial overload possibly due to decreased LA compliance after LA ablation was associated with AF recurrence after ablation [39].

Although a well experienced group reported a very high success rate of 80% after catheter ablation even in patients with congestive heart failure [40], the evidence described above suggests that catheter ablation alone is not sufficient to treat AF in patients with hemodynamic deterioration. This indicates that pharmacological therapies for heart failure, underlying cardiac pathophysiology, and hypertension, such as angiotensin-converting enzyme inhibitors, beta-blockers, statins, and diuretics, are as important as catheter ablation to decrease susceptibility to AF and to prevent recurrence of AF after ablation. Obesity and sleep apnea also affect hemodynamic status and are associated with the prognosis of AF. Continuous positive air pressure therapy (CPAP) may be effective for maintenance of sinus rhythm after ablation [41–43], but this needs to be tested by randomized prospective trials.

7. Advances in technology to isolate PVs

Standard 4-mm-tip ablation catheters were initially used for LA ablation. Because of the unstable and limited energy delivery of 4-mm-tip catheters due to the temperature-limited setting, 8-mm-tip catheters were introduced. However, one of problems in the use of 8-mm-tip catheters was the ambiguity of local electrograms due to the inclusion of far-field electrograms. Since 2000, irrigated-tip catheters have been used in European countries, and they offer several advantages, including delivery of the desired power independent of local blood flow [44]. The usefulness of this technology has been supported in animal models [45] and in patients undergoing ablation of AF [46,47].

Efforts continue to improve the efficacy and safety of LA ablation. Traditional catheter ablation is performed as a single-tip, point-by-point ablation process. This technique requires a high degree of operator skill, and procedures are lengthy, often lasting more than 4 h. Creating reliable continuous transmural lesions with a single-point catheter is difficult. During the past decade, a number of alternative ablation systems have appeared, including cryoablation (with a conventional-tip catheter or a circular catheter or balloon device), ultrasound ablation, laser ablation, and an over-the-wire multi-electrode catheter delivering duty-cycled bipolar and unipolar RF energy. A radiofrequency ablation catheter capable of real-time tissue–tip contact force measurements has recently been developed and has garnered particular attention. The contact force between the catheter tip and the tissue may affect the clinical outcome of RF ablation for the treatment of cardiac arrhythmias [48,49]. Insufficient contact force may result in an ineffective lesion, whereas excessive contact force may result in complications. Preliminary studies have indicated that a contact-force sensing catheter is useful for safe catheter manipulation and reduction of fluoroscopy time. In the future, it may also increase the effectiveness of ablations by allowing better control of the lesion size.

Although some of the modalities described are not currently available in Japan, we should keep in mind that advances in technology are as important as is understanding of the AF mechanism in clinical practice.

8. Ablation of persistent AF

Because triggers/drivers that originate from the PVs and other thoracic veins appear to be the primary mechanism of paroxysmal AF, ablation strategies that target only thoracic vein arrhythmogenicity have been effective in the majority of patients with paroxysmal AF. Additional linear ablation in combination with circumferential PVI resulted in an increased incidence of LA atrial tachycardia compared with circumferential PVI alone in patients with paroxysmal AF [50]. However, elimination of PV arrhythmogenicity alone has been insufficient to eliminate persistent AF. Although catheter ablation has also evolved into an effective treatment strategy in patients with persistent AF [46,47,51,52], the mechanism of persistent AF is still unclear and ablation efficiency remains low.

8.1. Efficacy of ablation of complex fractionated atrial electrograms (CFAEs)

Nademanee et al. performed ablation of AF that targets CFAEs, which are defined as electrograms with a cycle length of more than 120 ms, or shorter than that in the coronary sinus, or those that were fractionated or displayed continuous electrical activity [53]. Ablation of CFAEs resulted in termination of AF in ~95% of patients and an excellent clinical outcome, in which 90% of patients were reported to be free from recurrent arrhythmias. This ablation strategy is currently applied in combination with PVI because the clinical efficacy of ablation of CFAEs alone has been only modest, except in one study [53]. CFAE ablation in conjunction with PV antral isolation has a higher likelihood of maintaining sinus rhythm compared with PV antral isolation alone in patients with persistent AF [51]. Another randomized study showed that ablation of CFAEs after PV antral isolation did not have any incremental value over PV antral isolation alone [54]. The major problem concerning CFAE ablation is that the definition of CFAEs is arbitrary and subjective. The coexistence of the two fundamentally different types of electrograms that suggest different etiologies in one definition may not be appropriate for targeting a particular mechanism of AF. Although the authors of some studies tried to objectively detect CFAEs with custom software and demonstrate differences in the distribution of CFAEs in the LA between paroxysmal and persistent AF [55,56], the impact of the objective definition on clinical outcomes is unclear. The very high prevalence of CFAEs in the left atrium suggests that CEAEs alone are a nonspecific marker of appropriate target sites for ablation of AF [57]. Therefore, the value of CFAEs ablation remains controversial.

8.2. *Atrial tachycardia and efficacy of linear ablation*

Atrial tachycardia is common after catheter ablation of AF. Among a large number of patients undergoing circumferential PVI, the prevalence of atrial tachycardia at follow-up was reported to be 24% [24]. Forty-seven of 50 (94%) consecutive patients with mitral isthmus-dependent flutter following or during AF ablation had persistent AF as their primary arrhythmia [58]. Persistent AF is much more likely to convert to atrial tachycardia rather than to sinus rhythm during ablation. In 100 patients with persistent AF, atrial tachycardia comprised one-third of the recurrent arrhythmias after PV antral isolation in combination with CFAE ablation, and, notably, if patients had a critical decrease in the dominant frequency (DF) of AF of greater than 11% or had termination of AF during the procedure, the ratio of atrial tachycardia to total recurrent arrhythmia increased to 70% [3].

The majority of atrial tachycardias that occurred after circumferential PVI for AF were caused by a re-entrant mechanism. Mitral isthmus, roof, and septum accounted for 75% of the ablation target sites for macro-reentrant atrial tachycardias from the left atrium. The critical isthmus in 115 of 120 (96%) LA re-entrant atrial tachycardias traversed a prior ablation line, indicating that they were gap related [25]. There is, however, a hypothesis that the atrial tachycardia that occurs during catheter ablation of AF is a driver of AF that manifests after elimination of fibrillatory conduction [59]. Because both reports suggested a strong correlation between persistent AF and atrial tachycardia, prophylactic linear ablation accompanied by PVI may improve ablation outcome irrespective of whether AT is a cause or an effect. Retrospective evaluation found that linear ablations for macro-reentrant atrial tachycardia were required in the majority of patients with persistent AF even if persistent AF was terminated without linear ablation in the index procedure [60]. However, complete bidirectional block of the mitral isthmus usually requires aggressive ablation with a combined endocardial and epicardial approach. Interposition of the circumflex artery between the mitral isthmus and the coronary sinus is associated with a lower probability of achieving complete mitral isthmus block [61,62]. Particularly in such cases, this may result in a higher risk of complications such as cardiac tamponade and damage to the circumflex artery [63]. Assessment of the incremental value of linear ablations after PVI requires a randomized prospective study.

8.3. *Ablation endpoint*

Termination of AF during ablation is predictive of freedom from recurrent AF [46,47,64,65]. However, termination of persistent AF usually requires extensive ablation beyond the PVs, including ablation of CFAEs and multiple linear lesions. Extensive ablation is associated with long procedure time, radiation exposure, proarrhythmia, risk of collateral damage, compromise of LA transport function, and stiff LA syndrome. A multicenter prospective study showed the conflicting result that AF cycle length at baseline and termination of AF during ablation were not predictive of long-term sinus rhythm maintenance [66]. Another study showed that patient age and duration of radiofrequency energy were independent predictors of the outcomes after multiple procedures, whether or not the AF terminated during the procedure [67]. In a retrospective analysis of consecutive patients with persistent AF at the University of Michigan, a decrease in the dominant frequency of AF by 11% in response to PV antral isolation and ablation of CFAEs was associated with a probability of maintaining sinus rhythm that was similar to that when radiofrequency ablation terminated AF (Fig. 2) [3]. Appropriate patient selection and an endpoint tailored to each patient are essential for improvement of efficiency of catheter ablation of persistent AF.

9. The mechanism of persistent AF from the procedural point of view

The main explanation for the current disappointing ability to control AF is an incomplete understanding of the mechanism underlying its maintenance, despite many years of research and speculation. Over the past 50 years, the multiple wavelet hypothesis has been the dominant mechanistic model of AF. This hypothesis, first postulated by Moe et al., states that AF is the result of randomly propagating multiple electrical wavelets that interact in very complex ways, with local excitation limited by the heterogeneous distribution of refractory periods throughout the atria [68]. According to this model, the number of wavelets at any point in time depends on the atrial conduction velocity, refractory period, and mass. Perpetuation of AF is favored by slowed conduction, shortened refractory periods, and increased atrial mass. The shorter the wavelength is, the higher the number of wavelets there are. The presence of more wavelets makes perpetuation of AF more stable.

The so-called driver hypothesis has been posited in the recent years. Optical mapping studies in isolated sheep hearts have suggested that at least some cases of AF can be maintained by high-frequency reentrant sources (rotors), usually located in the posterior LA, which result in spatially distributed frequency gradients [69,70]. High-frequency rotors maintain AF through fibrillatory conduction to the remainder of the atria. From the clinical point of view, in patients with paroxysmal AF, this hypothesis is supported by the fact that high-frequency activity within the PV continues even after the restoration of sinus rhythm in the atria [71]. Presence of a left-to-right atrial frequency gradient in patients with paroxysmal AF also supports this hypothesis [72]. In persistent AF, however, electrophysiologists experience some responses of AF dynamics to ablation that are not consistent with the findings estimated from the driver hypothesis. For example, there is no left-to-right atrial frequency gradient in patients with persistent AF [72]. It is rare to find sites of DF_{max} in the PV region,

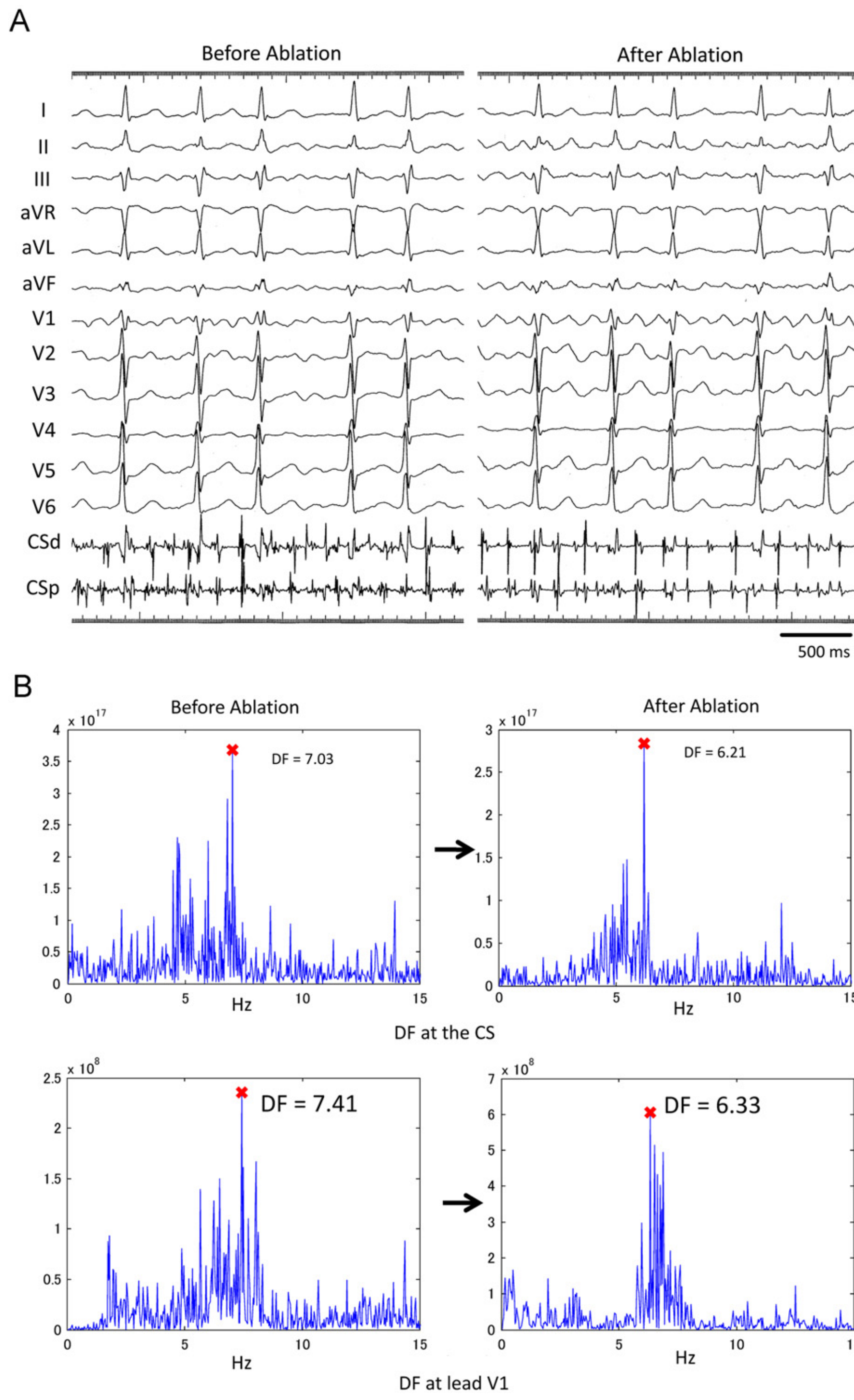

Fig. 2. Spectral analysis of atrial fibrillation. Electrograms recorded from the coronary sinus and lead V1 were processed, and the dominant frequency (DF) was determined by fast Fourier transformation. Shown are the 12-lead ECG (Panel A) and the periodograms (Panel B) at baseline and after radiofrequency catheter ablation. The DF in the coronary sinus (CS) decreased from 7.03 Hz to 6.21 Hz after ablation in this patient [58].

and isolated PV tachycardia after restoration of sinus rhythm in the atria has never been observed. A cumulative effect is frequently observed in ablation of persistent AF. Haïssaguerre et al. reported that although stepwise ablation was performed in a randomized order (PVI, atrial ablation, and coronary sinus/superior vena cava ablation), the number of patients with termination of AF increased as these procedural steps were completed [47]. It is a common finding that sites where radiofrequency application terminated AF had been previously ablated [73]. Taken together, it is difficult for the driver hypothesis alone to explain the findings observed during the procedure. One of the possibilities that can account for these findings might be the presence of multiple AF drivers, but this has not been proven in humans.

10. Complications

Because the major purpose of catheter ablation of AF is to improve patients' quality of life, and its efficacy in improving survival has not been proven, the probability and severity of complications related to AF ablation must be recognized by all electrophysiologists, and patients should only undergo AF ablation after carefully weighing the risks and benefits of the procedure. Because AF ablation is one of the most complex interventional procedures performed, the risk associated with this procedure is estimated to be higher than that of the procedures to treat other arrhythmias. Although prospective studies surveying the mortality rates associated with AF ablation procedures are lacking, a worldwide retrospective survey of prevalence and causes of fatal outcomes in AF ablation reported that lethal adverse events occurred in 0.1% of patients undergoing AF ablation [74]. Major causes of fatal outcomes were tamponade, stroke, and atrioesophageal fistula. More recently, predictors of complications and 30-day readmissions were identified from the data from the California State Inpatient Database [75]. Five percent of patients experienced periprocedural complications, and almost 10% were rehospitalized within 30 days. One patient died during the index admission, and 9 patients died during the 30-day rehospitalization, resulting in a mortality rate of 0.24%. These rates are quite high when one considers that AF itself is not a life-threatening arrhythmia.

Because a delay in the diagnosis of tamponade is fatal, continuous monitoring of systemic arterial pressure during and following AF ablation is mandatory. Although the majority of episodes of tamponade can be managed by immediate percutaneous drainage, surgical drainage and repair are sometimes needed. Thus, AF ablation should only be performed in hospitals equipped to provide emergency surgical support when required.

Oral et al. reported that AF ablation is associated with early postprocedure thromboembolism, regardless of both the post-procedure rhythm and whether the patient has risk factors for stroke. The most likely cause was thought to be char and/or thrombus formation at sites of LA endocardial ablation, and the probability was 1.0% [76]. Thus, heparin anticoagulation with close attention to maintaining a therapeutic dose (activated clotting time (ACT) of at least 300–350 s) during the procedure is important. Data regarding the risk of thromboembolism with and without warfarin after AF ablation is limited. Because symptomatic or asymptomatic AF may recur during long-term follow-up after an AF ablation procedure [31], discontinuation of warfarin therapy post-ablation generally is not recommended in patients who have a CHADS2 score ≥ 2 [6]. Although the use of dabigatran has increased in clinical practice, an observational study with a matched-control design reported that periprocedural dabigatran use significantly increased the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy in patients undergoing AF ablation [77]. Large randomized controlled studies are required to confirm this result.

Development of an atrial–esophageal fistula is one of the most dreaded complications of AF ablation [78]. A relatively large-scale nonrandomized study revealed that the anatomical risk factor of a small LA-to-esophageal distance was the most important factor in esophageal ulceration when using an irrigation-tip catheter at an energy setting of $\sim$25 W at the posterior left atrium. Most of the patients who developed an atrial–esophageal fistula in this study died (7/9 patients, 78%) [74], and it is vital to avoid this complication. The most common practice is to decrease power delivery, decrease tissue contact pressure, and move the ablation catheter every 10–20 s when in close proximity to the esophagus. A number of other approaches are also used to avoid the development of an atrial–esophageal fistula [79–84], including temperature monitoring of the esophagus, use of pain as an assay for potential esophageal injury, the use of capsule endoscopy after AF ablation, and mechanical displacement of the esophagus during the AF procedure. Yamasaki et al. showed that low body mass index is a predictor for esophageal injury even at low energy settings of radiofrequency delivery [85]. Because Asian people are generally thinner than people in other regions of the world, the risk of esophageal injury must always be considered in each patient undergoing ablation of AF.

11. Future direction

The mechanisms of AF are very complex and even somewhat mysterious. While it may not be easy to attain a greater understanding of the mechanism of AF or to discover clearer guidance on catheter ablation, research on AF nonetheless leads to a better understanding of other cardiac and non-cardiac diseases because AF develops multifactorially in association with various underlying systemic pathophysiologies. To understand AF is to understand the whole body. It is our goal and hope as a next step to promote catheter ablation as a first-line therapy in more patients with AF based on definitive evidence that the procedure reduces mortality and morbidity.

Conflict of interest

All authors have no conflict of interest to declare.

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